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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,678	05/14/2008	Yoshihide Hayashizaki	035576.301942	9684

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,678	HAYASHIZAKI ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/25/9; 6/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restriction

In the Reply of 10/8/10, Applicant elected, with traverse, Group 1 and the species: aldehyde dehydrogenase. The traversal is on the ground(s) that searching all groups would not impose a serious burden on the examiner. These arguments have been considered but are not found persuasive as such arguments do not apply when restriction is required under 35 USC 121 and 372, as in the instantly filed application. Thus, when the Office considers international applications as an International Searching Authority, as an International Preliminary Examining Authority, and during the national stage as a Designated or Elected Office under 35 U.S.C. 371, PCT Rule 13.1 and 13.2 will be followed when considering unity of invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111.

Claims 1-5 are pending.

Claims 3-5 are withdrawn.

Claims 1-2 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting metastatic cancer cells originating from gastric cancer comprising collecting ascites fluid sample from a subject and detecting the presence of aldehyde dehydrogenase mRNA in the sample, wherein the presence of aldehyde dehydrogenase mRNA in the sample indicates the presence of metastatic cancer cells originating from gastric cancer in the sample, **the specification does not reasonably provide enablement for** a method of detecting metastatic cancer cells originating from gastric cancer comprising collecting just any biological sample from a subject and detecting the presence of aldehyde dehydrogenase mRNA or protein in the sample, wherein the presence of aldehyde dehydrogenase mRNA or protein in the sample indicates the presence of metastatic cancer cells originating from gastric cancer in the sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to a method of detecting metastatic cancer cells originating from gastric cancer comprising collecting just any biological sample from a subject and detecting the presence of aldehyde dehydrogenase mRNA or protein in the sample, wherein the presence of aldehyde dehydrogenase mRNA or protein in the sample indicates the presence of metastatic cancer cells originating from gastric cancer in the sample. This includes methods wherein detection of any amount of aldehyde dehydrogenase mRNA or protein in just any biological sample from a subject is indicative of metastatic cancer cells originating from gastric cancer in the sample.

This invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The specification teaches a method of detecting metastatic cancer cells originating from gastric cancer comprising collecting ascites fluid sample from a subject and detecting the presence of aldehyde dehydrogenase mRNA in the sample, wherein the presence of aldehyde dehydrogenase mRNA in the sample indicates the presence of metastatic cancer cells originating from gastric cancer in the sample (see page 20, in particular). The specification does not demonstrate detection of any amount of aldehyde dehydrogenase mRNA or protein in just any biological sample from a subject is indicative of metastatic cancer cells originating from gastric cancer in the sample.

The level of unpredictability for using a particular expression pattern of a particular molecule to detect any disease is quite high. The state of the prior art dictates that one of skill in the art would not predict that a particular expression pattern of a

particular molecule is indicative of a particular diseased state without a demonstration that said particular diseased stated correlates with said particular expression pattern of said particular molecule. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Absent evidence demonstrating a particular expression pattern of a particular molecule correlating with a particular diseased state, one of skill in the art would not predict said particular expression pattern of said particular molecule correlates with said particular diseased state without undue experimentation. Experimentation to identify such a correlation would in itself be inventive.

In regards to the unpredictability of using aldehyde dehydrogenase protein as a marker for metastatic gastric cancer, evidence abounds in which protein levels do not correlate with alterations in mRNA levels. There are many steps in the pathway leading from DNA to protein, and all of them can, in principle, be regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Further, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have

tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Further, an example wherein a change in mRNA level of a gene accompanying a phenotypic change is not accompanied by a change in protein level of said gene is taught by Lichtinghagen et al (European Urology, 2002, 42:398-406). Lichtinghagen et al teaches MMP-2 mRNA expression is decreased in cancerous tissue compared to corresponding normal tissue; however, this decrease in MMP-2 mRNA expression is not accompanied by a decrease in MMP-2 protein

expression (see Abstract and Figures 2-3, in particular). Lichtinghagen et al further teaches MMP-9 protein is increased in cancerous tissue compared to corresponding normal tissue; however, this increase is not accompanied by an increase in MMP-9 mRNA (see Abstract and Figures 2-3, in particular). Lichtinghagen et al further teaches TIMP-1 protein is decreased in cancerous tissue compared to corresponding normal tissue; however, this decrease is not accompanied by a decrease in TIMP-1 mRNA (see Abstract and Figures 2-3, in particular). Thus, due to the multitude of homeostatic factors affecting transcription and translation, protein levels do not predictably correlate with levels of mRNA (and vice-versa).

In regards to the unpredictability of using just any presence of aldehyde dehydrogenase in just any sample a marker for metastatic gastric cancer, Jelski et al (Dig Dis Sci, 2007, 52: 531-535) demonstrates that alcohol dehydrogenase (ALDH) activity is present in healthy tissue (see Table 1, in particular). Therefore, one of skill in the art would not predict that just any presence of aldehyde dehydrogenase in just any sample is indicative of metastatic gastric cancer.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods wherein just any presence of aldehyde dehydrogenase mRNA or protein in just any sample from a subject indicates the presence of metastatic cancer cells originating from gastric cancer in the sample, and Applicant has not enabled said methods because it has not been shown that just any presence of aldehyde dehydrogenase mRNA or protein in just any sample from a

subject indicates the presence of metastatic cancer cells originating from gastric cancer in the sample.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, and the teaching that aldehyde dehydrogenase is active in normal tissues, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2 are rejected under 35 U.S.C. 102(a) as being anticipated by Sakakura et al (British Journal of Cancer, 2002, 87(10): 1153-1161).

Sakakura et al teaches a method comprising collecting a biological sample from a subject and detecting the presence of aldehyde dehydrogenase mRNA in the sample; and determining that the possibility of containing metastatic cancer cells originating from gastric cancer is high when aldehyde dehydrogenase mRNA is present (Figure 4, in particular).

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642